

## First Take

### Prana Biotechnology Limited (PRAN)

February 18, 2014

Price: \$9.70; Market Cap (MM): \$379

Rating: Buy; Price Target: UR

*Intraday*

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### Reach2HD Results Beat Expectations; Unexpected Significant Difference in Key Cognitive Measure

**Reach2HD Results Better Than Expected:** This morning we initiated coverage of Prana Biotechnology Ltd. on the premise that IMAGINE, an ongoing Phase IIa trial of the company's leading drug candidate, PBT2, in Alzheimer's disease (AD), was likely to deliver positive top line results within weeks. Indeed, Prana publicly guided to announcing results in mid-March. Concurrently, Prana conducted a signal-seeking, Phase IIa trial of PBT2 in Huntington's disease (HD) called Reach2HD. On Feb. 17 in Australia, Prana was granted a request to halt trading in its stock on the Australian markets pending an announcement of the Reach2HD results. We wrote in our initiation report that the results were likely to be released today, tomorrow at the latest. The results were indeed released this morning and they beat our expectations.

**Objectives of Reach2HD:** It is important to review the objectives of Reach2HD. We emphasize that this was first and foremost a *safety trial* and secondly an *efficacy signal-seeking trial*, meaning that the trial incorporated multiple efficacy measures of motor, cognitive, and behavioral disturbances in HD. The objective was to *identify improving trends* that would be used as primary efficacy endpoints in a confirmatory Phase IIb trial before advancing to a registrational Phase III trial. Due to the small size of Reach2HD, it is important to understand that *statistical significance of any efficacy parameter was NOT expected*.

**Significant Difference in a Key Cognitive Measure Seen:** Reach2HD showed a statistically significant difference between the placebo and high dose (250 mg) PBT2 group in an important cognitive measure called the Trail Making Test Part B (TMTB). After 6 months of treatment, the time to complete an assigned task *increased* by 14 seconds in the placebo group, while patients in the PBT2 group showed a *decrease* of 4 seconds to complete the task. In other words, performance in the placebo group worsened (as expected) while improving marginally in the PBT2 treated group. In our view, this was an unexpected finding, but very important because the TMTB test, among other tests of cognition, has been well documented to be able to distinguish between prodromal HD and neurologically normal individuals. Of the several cognitive tests used in Reach2HD, we think the TMTB was the *most important one* in which to observe a difference.

**Bonus on Brain Volume:** A steady decrease in brain volume is observed with HD disease progression. Brain volumes were measured in 6 patients in Reach2HD. Cortical thinning occurred at a faster, but not statistically significant, rate in 2 patients than in 4 PBT2 treated patients. Notably, others have shown that TMTB scores correlate with brain volume changes in prodromal HD, thus demonstrating internal consistency in the Reach2HD results, albeit in a small number of patients. Importantly, changes in cognitive reserve, an accepted measure of HD progression, was associated with TMTB and brain volume loss, again underscoring the importance of the TMTB test.

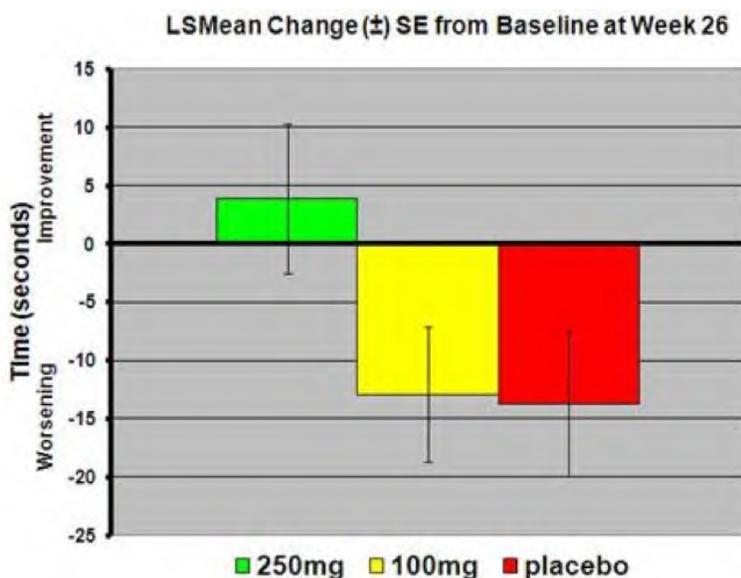
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**One-Year Price Target Under Review; Maintaining Our BUY Rating:** We wrote in our initiation report that due to the lack of preclinical and early stage clinical trial evidence supporting the use of PBT2 in HD, that we did not have as much confidence in a positive outcome as we had for IMAGINE, the AD trial. Consequently, we based our BUY rating and one-year price target solely on the AD indication, adding that positive results in Reach2HD would be an unexpected bonus for Prana investors. The Reach2HD results announced today will prompt us to review our one-year price target for Prana, but we are maintaining our BUY rating as our outlook for the outcome of the IMAGINE trial in AD, upon which we based our prior rating and price target, is essentially unchanged. We intend to participate in Prana's webcast ([www.pranabio.com](http://www.pranabio.com)) and conference call (dial: 855-293-1544; conference ID: 58817510) scheduled for this afternoon at 5:30 pm ET. We will update our model and one-year price target based on what more is said on the conference call about Reach2HD results and the company's guidance regarding the next steps in the further development of PBT2 for HD.

**Prana's Press Release:** This morning's press release announcing the results of Reach2HD can be accessed here:

<http://pranabio.com/news/prana-announces-successful-phase-2-results-huntington-disease-trial#.UwOJkKPJQU>

**Changes in TMTB Performance:** The TMTB consists of 25 circles randomly drawn on a sheet of paper. The circles contain numbers (1-13) and letters (A-L). The task in TMTB is to draw lines connecting the circles in ascending order, alternating numbers and letters (1-A-2-B-3-C-etc.). The TMTB is a well-documented measure of executive function, processing speed, and working memory. Performance on the TMTB in Reach2HD is shown below for the three treatment groups. There were 35, 38, and 36 patients in the placebo, 100 mg PBT2, and 250 mg PBT2 groups. The difference between the placebo and 250 mg PBT2 groups was statistically significant with a p-value of 0.042.



Neurologically normal individuals can complete the TMTB with no errors in about 75 seconds. Neurologically deficient individuals take longer than 4 1/2 minutes to complete the task, often with errors.

Source: Press release: "Prana Announces Successful Phase 2 Results in Huntington Disease Trial", Prana Biotechnology Ltd., February 18, 2014.

## Important Disclaimers

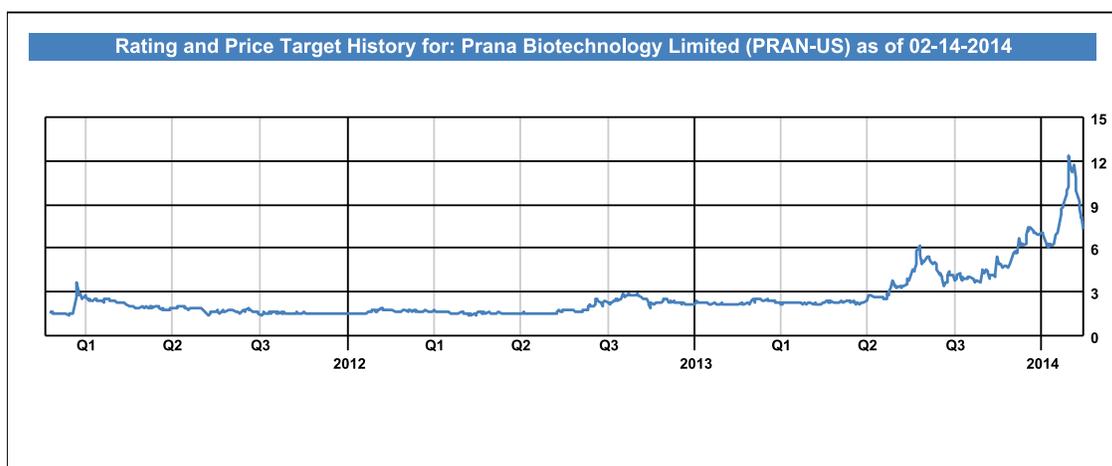
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Distribution of Ratings Table				
Ratings	Count	Percent	IB Service/Past 12 Months	
			Count	Percent
Buy	28	87.50%	9	32.14%
Neutral	1	3.12%	0	0.00%
Sell	0	0.00%	0	0.00%
Under Review	3	9.38%	0	0.00%
<b>Total</b>	<b>32</b>	<b>100%</b>	<b>9</b>	<b>28.12%</b>

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